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Green Protocol for the Synthesis of 2, 4, 5-Trisubstituted Imidazole Derivatives Catalyzed by Copper Oxide Nanoparticles (Copper Oxide NPs)

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Abstract: *A facile, efficient and one pot synthesis of 2, 4, 5-trisubstituted imidazole derivatives via the condensation of benzil, substituted benzaldehydes and ammonium acetate using copper oxide NPs in presence of ethanol as a solvent under reflux. Copper oxide NPs is an effective catalyst and easy for separation. Copper oxide NPs also as a green catalyst, low cost, environmental friendly catalyst used for these reaction carried out under reflux. The remarkable advantages of this methodology are simple operation, short reaction time, clean reaction ways and high to excellent yield of product. The synthesized Copper oxides NPs are characterized by UV-Visible spectra, X-ray Diffraction (XRD) and Field Emission-Scanning electron microscopy (FE-SEM) analysis. In UV-visible spectra, a peak was obtained at 427.50 nm due to inter band transmission of core electron. The pattern of XRD analysis showed particle size of 25-85 Nm and it reveals high crystallinity of the Copper oxide NPs. In FE-SEM, the average size of synthesized nanoparticles is about 55 nm according to measurement software.*

Keywords: Benzil, Substituted benzaldehyde, Ammonium acetate, Copper oxide NPs.

I. INTRODUCTION

Imidazole and their derivatives are important heterocyclic compounds because of their synthetic utility and their broad range of synthetic, biological and medicinal applications. Imidazole and their derivatives were used for the synthesis of various types of medicinal compounds having a good therapeutic values such as antimicrobial [1-2], anti-HCV [3], anti-tumor [4], Leishmanicidal [5], anti-convulsant [6], GABA up take inhibitory [7], cytotoxic [8-9], anti-cancer [10], anti-proliferative [11-12], anti-tubercular [13], antifungal [14-15], anti-candidal activity [16], anti-bacterial [17-18], anti-inflammatory [19-20], Therapeutic activity [21], and anti-viral [22-23] activities etc. The some various substituted imidazole acts as plant growth regulators [24], p38α MAP Kinase Inhibitors [25], β-Raf Kinase [26], Glucagon receptors [27], anti-amoebic activity [28] etc.

In recent years, numerous methods have been developed for the synthesis of 2, 4, 5-trisubstituted imidazole using various catalyst including Sulfuric Acid Immobilized on Silica Gel [29], Ceric Ammonium Nitrate [30], L-Proline [31], $ZrCl_4$ [32], a Metal–Organic Framework $Cu_2(BDC)_2(DABCO)$ [33], $KMnO_4/CuSO_4$ [34], PEG-400 [35], benzyltriphenylphosphonium chloride (BTPPC) [36], 3-picolinic acid [37], HNO_3 in Microwave irradiation [38], Indium (III) Triflate and Magnesium Sulfate Heptahydrate [39], Fe_3O_4 and Cu_2O nanoparticles [40], Fly Ash Supported Bi_2O_3-ZnO [41] etc.

Copper oxide NPs are eco-friendly, less expensive catalyst and its many biological and medicinal activities [42]. Copper oxide NPs can be prepared in low concentration of Azadirachta indica (Neem) leaf extract without using any additional harmful chemical methods [43].

In the present work, an efficient synthesis of 2, 4, 5-trisubstituted imidazole derivatives by the condensation of benzil, various substituted benzaldehyde and ammonium acetate using Copper oxide NPs as a catalyst in presence of ethanol under reflux.

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II. Material and Methods

Melting point of synthesized compounds were determined by melting point apparatus with an open capillary tubes and were uncorrected. All the chemicals were of analytical reagent (AR) grade purchased from commercial suppliers were used as without further purification. Used Copper oxide NPs as a catalyst were characterized by microscopic and spectroscopy techniques such as UV-Visible spectroscopy, X-ray Diffraction and Field emission-scanning electron microscope (FE-SEM). All the synthesized compounds were well known and identified by comparing with melting point, FT-IR, ^{1}H-NMR, ^{13}C-NMR, and Mass analysis (LC-MS). The FT-IR spectroscopy were recorded on SHIMADZU FT-IR 8400 using KBr pallets. The ^{1}H-NMR and ^{13}C-NMR spectroscopy were recorded in $CDCl_3$/DMSO-d^6 on BRUCKER-400 MHz and Mass analysis spectra were recorded on SHIMADZU MODEL-8045 at ESI-APCI interface.

2.1 Preparation of Plant Extract

Azadirachta indica (Neem) fresh leaves were collected in rural area, washed with distilled water and leaves were dried with absorbent paper. These leaves were cut into small pieces and about 25 g chopped Neem leaves were weighted and taken in a beaker. About 250 mL of distilled water was added to it. This was heated for 1 h at 60 °C. By this time, aqueous part turns yellow. The plant extract was filtered by Whatman no.1 filter paper to remove unwanted impurities. This filtrate was made up to 250 mL in a standard measuring flask. It was then stored in refrigerator for further use.

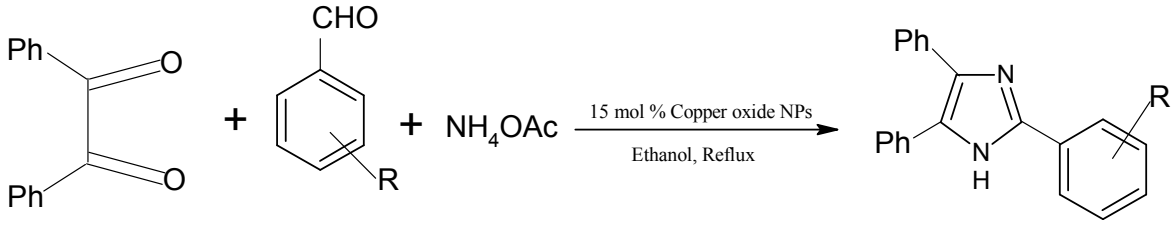
2.2 General Procedure for the Synthesis of Copper oxide NPs

About 4.99 g of copper acetate salt was weighted accurately and diluted up to 250 mL in water. Then 50 mL of above copper acetate solution and 150 mL of Neem plant extract were taken and mixed in a beaker for the synthesis of Copper oxide nanoparticles. When mixed it is observed that the dark green brown colored precipitate is settling down in a beaker. This obtained precipitate was filtered using Whatman no.1 filter paper to remove particulate matter. Solid precipitate washed many times with distilled water and left overnight to dry. The next day Copper oxide NPs are collected [44].

General Procedure for the Synthesis of 2, 4, 5-Trisubstituted Imidazole Derivatives:

In a clean 100 mL RBF, take a benzil (1 mmol), substituted benzaldehyde (1 mmol), ammonium acetate (3 mmol) and 15 % mol Copper oxide NPs as a catalyst was added in presence of ethanol at 80 °C under reflux. The progress of reaction was checked by TLC on silica gel coated Al-sheets in a solvent (n-hexane: Ethyl acetate-1:4). After completion of reaction, the mixture was diluted with ethanol (20 mL) and catalyst was separated by filtration. The solid imidazole product was filtered, washed and recrystallized from ethanol.

2.3 Scheme



2.4 Spectral Analysis

1a] 2, 4, 5-Triphenyl-1H-Imidazole. White solid, M.P- 272-273 °C.

FT-IR (KBr, cm^{-1}):- 3062.42, 1659.38, 1594.58, 1460.73, 1210.74, 1127.66, 765.48, 697.03. ^{1}H-NMR (400 MHz, DMSO-d^6):- δH 11.835 (s, 1H, NH), δH 8.008-7.215 (m, 15H, ArH). ^{13}C-NMR (DMSO-d6):- δC 194.63, δC 146.31, δC 134.95-125.55. LCMS *m/z*: calculated for [$C_{21}H_{16}N_2$] 297.0, observed 297.40.

1b] 2-(4-Hydroxyphenyl)-4, 5-diphenyl-1H-Imidazole. White solid, M.P- 234-235 °C.

FT-IR (KBr, cm^{-1}):- 2969.30, 2722.69, 1456.79, 1359.0, 1167.55, 973.34, 841.54, 808.68. ^{1}H-NMR (400 MHz, DMSO-d6):- δH 9.366 (s, 1H, NH), δH 7.846 (d, 2H, ArH), δH 7.470 (d, 2H, ArH), δH 7.452-6.753 (m, 10H, ArH). ^{13}C-NMR

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(DMSO-d6):- δC 158.0, δC 146.67, δC 128.38-126.98, δC 115.58. LCMS *m/z*: calculated for [$C_{21}H_{16}N_2O$] 313.0, observed 312.40.

1c] 2-(4-Chlorophenyl)-4, 5-diphenyl-1H-Imidazole. White solid, M.P- 258-260 °C.
FT-IR (KBr, cm^{-1}):- 3522.84, 1695.80, 1591.12, 1486.05, 1328.11, 1186.37, 1089.69, 979.12, 823.67, 701.88. ^{1}H-NMR (400MHz, $CDCl_3$/DMSO-d6):- δH 9.366 (s, 1H, NH), δH 7.852 (d, 2H, ArH), δH 7.831 (d, 2H, ArH), δH 7.554-7.265 (m, 10H, ArH). C^{13}-NMR ($CDCl_3$/DMSO-d6):- δC 145.04, δC 133.47, δC 129.34-126.95. LCMS *m/z*: calculated for [$C_{21}H_{16}N_2Cl$] 331.0, observed 330.80.

III. Results and Discussion

To optimize the reaction conditions, the synthesis of 2, 4, 5-trisubstituted imidazole derivatives by the reaction of benzil, substituted benzaldehyde and ammonium acetate using Copper oxide NPs as a catalyst in presence of ethanol under reflux. The result is obtained in table 1, shows that amongst the different type of solvents investigated under reflux, ethanol is excellent solvent to higher yield of expected product. In table-2 shows the amount of catalyst used for these synthesis to obtain maximum yield. We have carried out reactions in different amount of catalyst and the yield of product is increased. It is found that 15 % mole of catalyst is sufficient, further increasing the amount of catalyst does not affect the percentage yield of product. Under the optimized reaction condition, various substituted benzaldehydes were reacted with benzil and ammonium acetate to obtained 2, 4, 5-trisubstituted Imidazole. In all the cases, reactions were completed in a reasonable time and Imidazole derivatives were formed in high yield is as shown in table 3.

Copper oxide NPs acts as a heterogeneous nano catalyst for the synthesis of 2, 4, 5-trisubstituted imidazole derivatives. The reaction of benzil, substituted benzaldehyde and ammonium acetate in presence of ethanol under reflux. This procedure generated a collection of functionalized imidazole derivatives with grater position of functional group for both electron withdrawing or donating groups. It was observed that, electron donating substituents attached to benzaldehyde decrease the rate of reaction with less yield of product (Table-3, 1h) while electron withdrawing groups attached to benzaldehyde increase the rate of reaction with higher yield of expected product (Table-3, 1d and 1g) as shown in table 3.

Table 1: Screening of Solvents for the Synthesis of 2, 4, 5-Trisubstituted Imidazoles

Sr. No.	Solvents	% mole of catalyst	Time (min)	Temp(°C)	Yield
1	Chloroform	5	60	80	40%
2	DMSO	5	60	80	34%
3	Solvent free	5	60	80	20%
4	Acetonitrile	5	60	80	27%
5	Dichloromethane	5	60	80	31%
6	Tetrahydrofuran	5	60	80	43%
7	Methanol	5	60	80	46%
8	Ethyl acetate	5	60	80	38%
9	Toluene	5	60	80	41%
10	**Ethanol**	**5**	**60**	**80**	**58%**

Table 2: Effect of % Mole of Catalyst for the Synthesis of 2, 4, 5-Trisubstituted Imidazoles.

Sr. No.	Solvent	% mol of Catalyst	Time (min)	Temp(°C)	Yield
1	Ethanol	5 %	60	80	62 %
2	Ethanol	10 %	40	80	78 %
3	**Ethanol**	**15 %**	**20**	**80**	**96 %**
4	Ethanol	20 %	20	80	96 %
5	Ethanol	30 %	20	80	96 %

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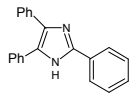
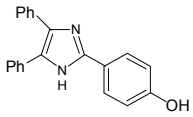
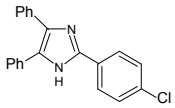
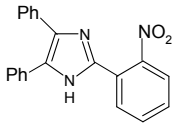
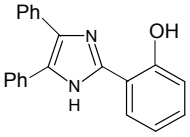
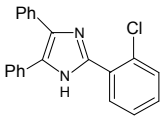
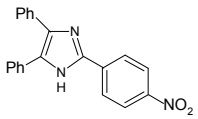
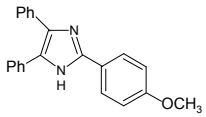
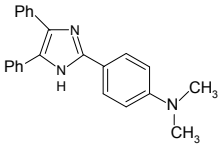
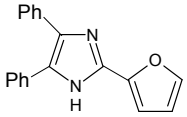
Table 3: Copper Oxide NPs Catalyzed by Synthesis of 2, 4, 5-Trisubstituted Imidazole Derivatives.

Entry	R-Ar-CHO	Product	Time (min)	Yield (%)	M.P (°C)
1a	Ar-H		20	96	272-273
1b	4-OH-Ar-CHO		20	96	234-235
1c	4-Cl-Ar-CHO		20	96	258-260
1d	2-NO_2-Ar-CHO		20	96	298-300
1e	2-OH-Ar-CHO		20	96	209-210
1f	2-Cl-Ar-CHO		20	96	193-194
1g	4- NO_2-Ar-CHO		20	96	199-201
1h	4-OCH_3-Ar-CHO		20	95	227-229
1i	4-Dimethylamino-Ar-CHO		20	95	257-258
1j	Furfur aldehyde		20	96	200-202

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3.1 Characterization of Catalyst

A. UV-Visible Spectral Analysis

UV-visible spectral analysis of Copper oxide NPs was done in the wavelength range of 200-800 nm. A peak was obtained at 427.50 nm due to inter band transition of core electrons of Copper oxide NPs and the spectrum was represented as fig 1

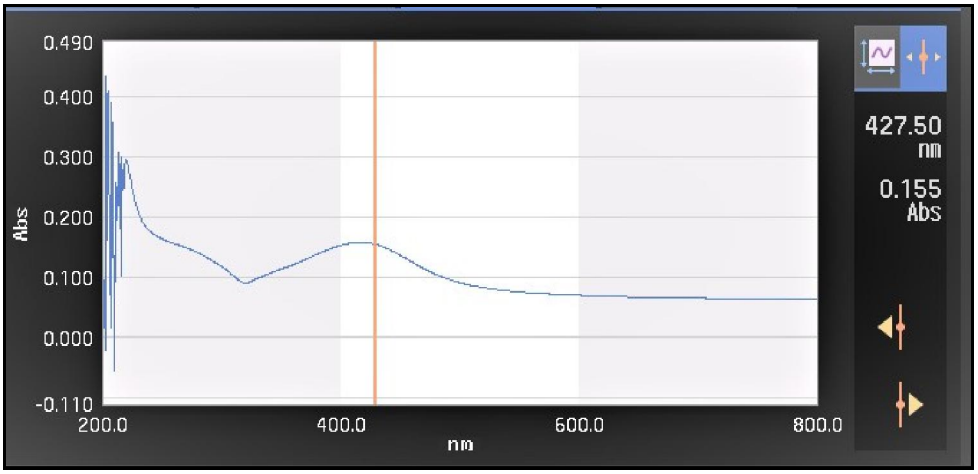

Figure 1: UV-visible analysis of Copper oxide NPs.

B. X-Ray Diffraction Analysis

The formation of the Copper oxide NPs was further confirmed by the X-ray diffraction analysis. The XRD pattern of Copper oxide NPs using a leaf extract of Azadirachta indica (Neem) is as shown in fig 2. The XRD pattern shows a high crystallinity of sample level with diffraction angle 2θ values of 20.53^0, 31.52^0, 42.20^0, 62.10^0 with corresponding h, k, l values to the reflection from (111), (200), (220) and (222) resp. The XRD pattern of the Copper oxide NPs is crystalline and identical to simple cubic.

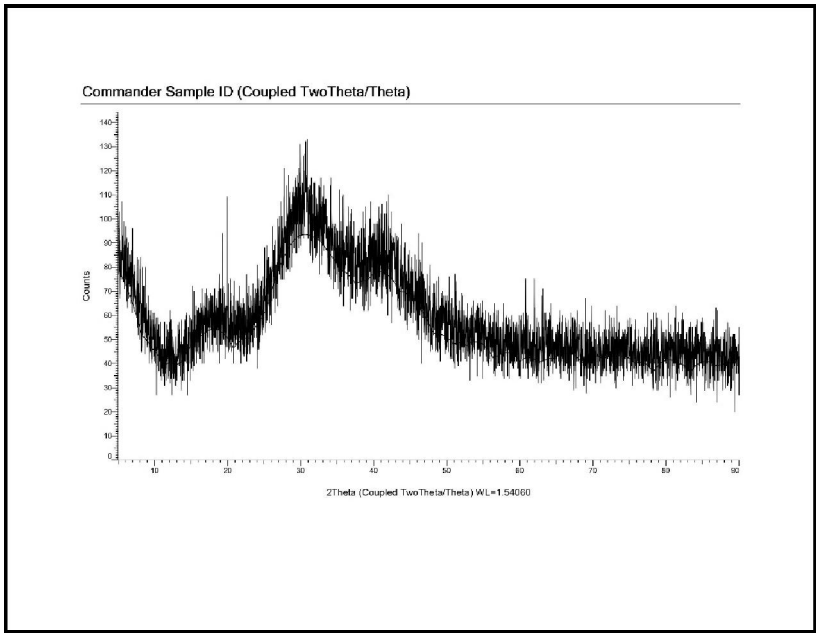

Figure 2: XRD pattern of Copper oxide NPs.

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C. Field Emission-Scanning Electron Microscope (FE-SEM) Analysis

To study size and shape of the prepared Copper oxide NPs, FE-SEM analysis was carried out. The FE-SEM image of catalyst proved its spherical in shape is as shown in fig 3. The average size of synthesized Copper oxide NPs is about 25-85 nm according to measurement software

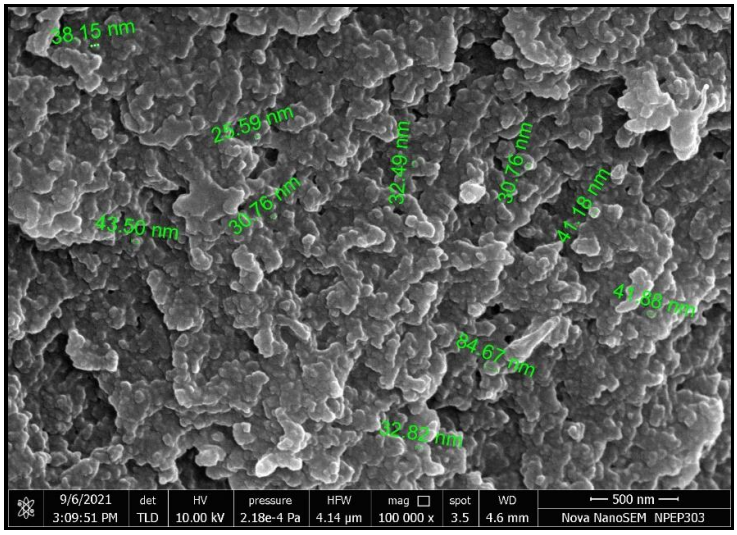

Figure 3: FE-SEM analysis of copper oxide NPs.

IV. Conclusion

In summary, we have prepared Copper oxide NPs by using Azadirachta indica (Neem) extract and found to be a cheap, clean and efficient catalyst for the synthesis of 2, 4, 5-trisubstituted imidazole derivatives by condensation of benzil, ammonium acetate with substituted benzaldehyde in presence of ethanol under reflux. The simplicity of this method includes its simplicity of operation, clean reaction condition, high to excellent yield of product and lower reaction time. The Copper oxide NPs catalyst is easy for separation, non-toxic, eco-friendly, low waste and environmentally safe.

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Conflicts of Interest: The authors declare no conflict of interest.

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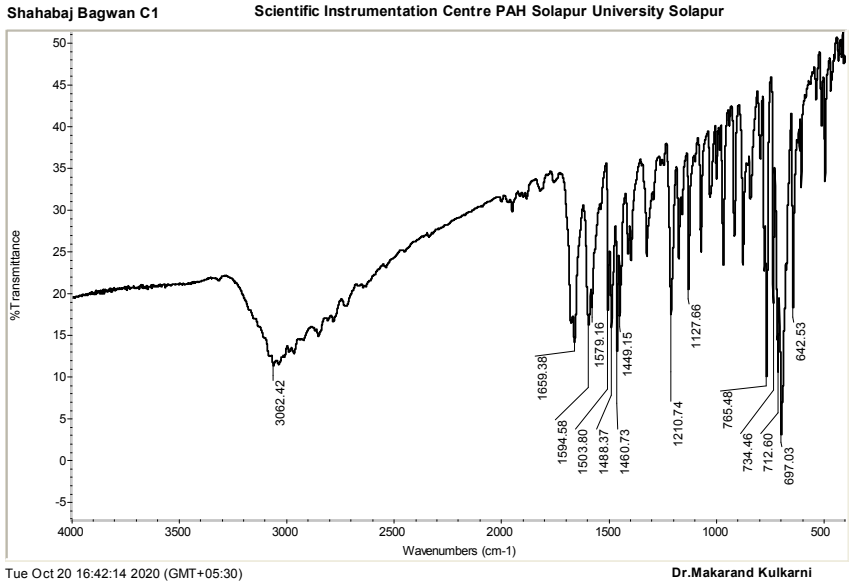
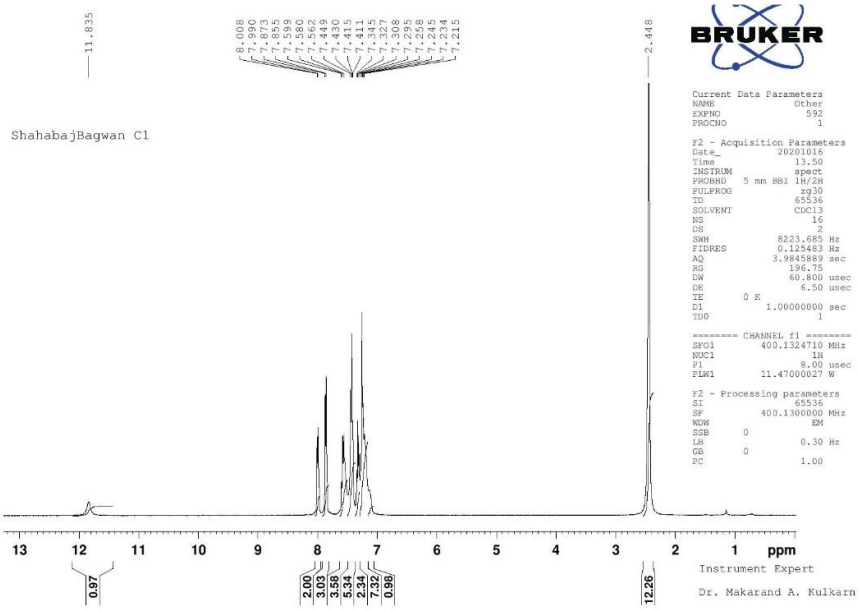
Spectroscopic Analysis:

A. FT-IR Analysis of 2, 4, 5-Triphenyl-1H-imidazole (1a):



B. ^{1}H-NMR Analysis of 2, 4, 5-Triphenyl-1H-imidazole (1a):



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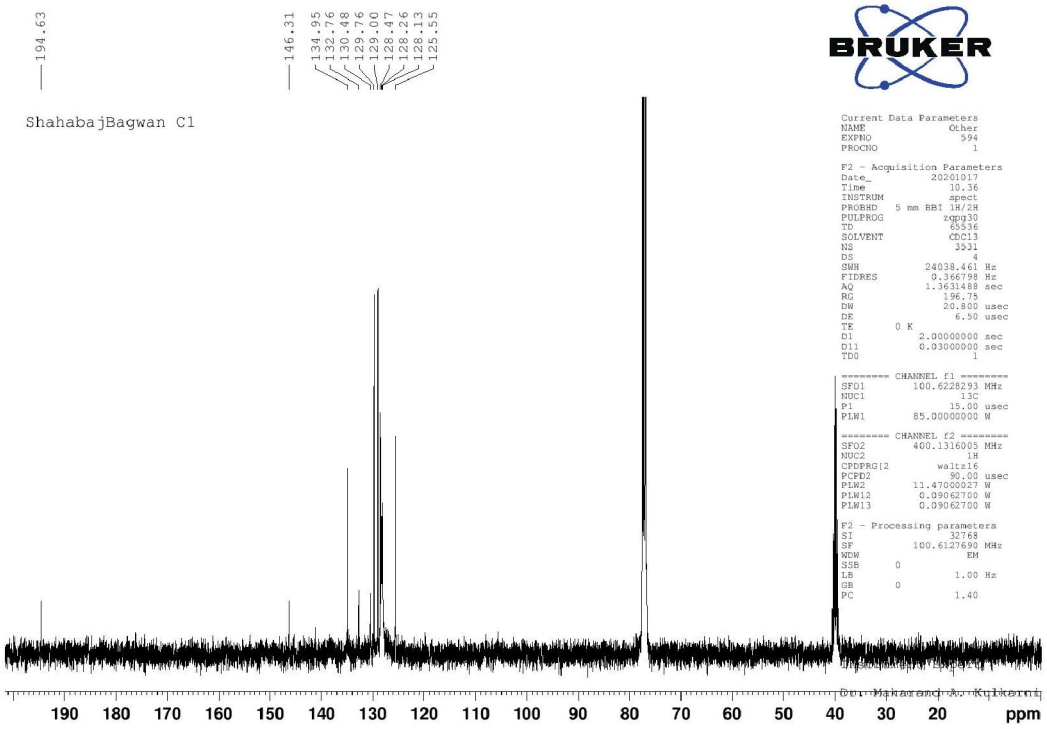
C. ^{13}C-NMR Analysis of 2, 4, 5-Triphenyl-1H-imidazole (1a):



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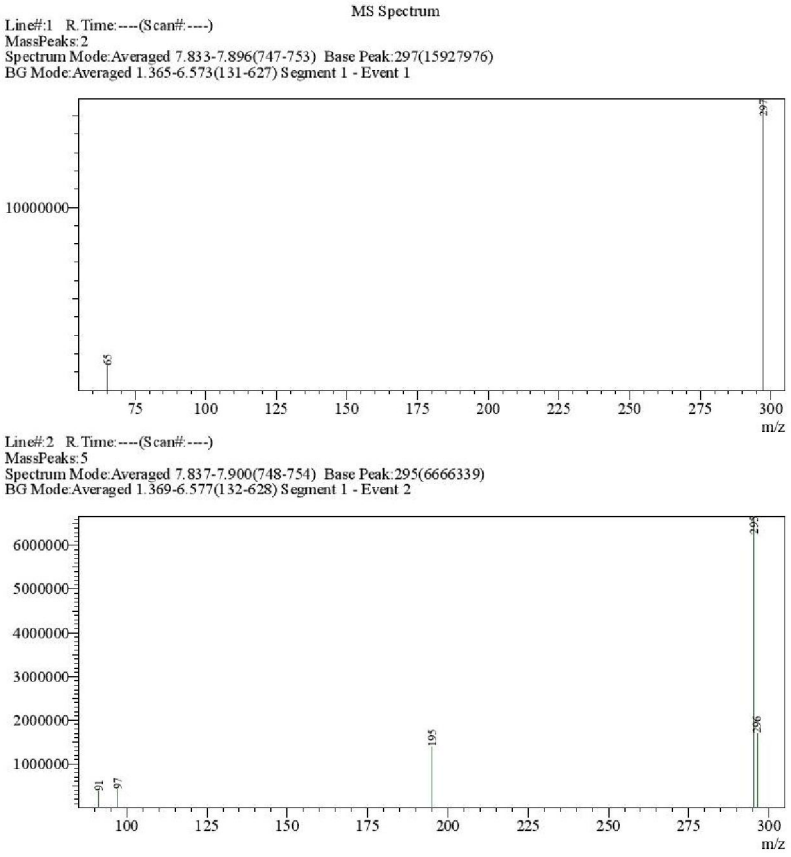
D. Mass Analysis of 2, 4, 5-Triphenyl-1H-imidazole (1a):

SOPHISTICATED ANALYTICAL INSTRUMENT FACILITY (SAIF)
M.G.UNIVERSITY, KOTTAYAM

Summary(Data)

Sample Name	**: Sample C**
Vial#	**: 46**
Injection Volume	**: 5**
Month-Day Acquired	**: 10/8/2020**
Time Acquired	**: 11:24:41 AM**
Comment	**:**



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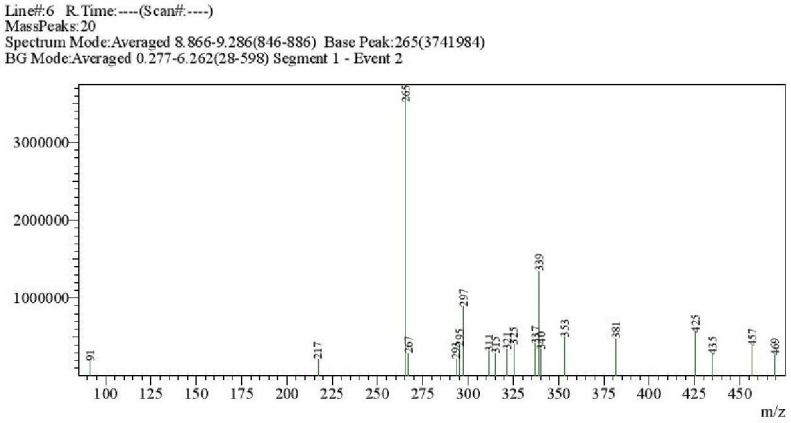

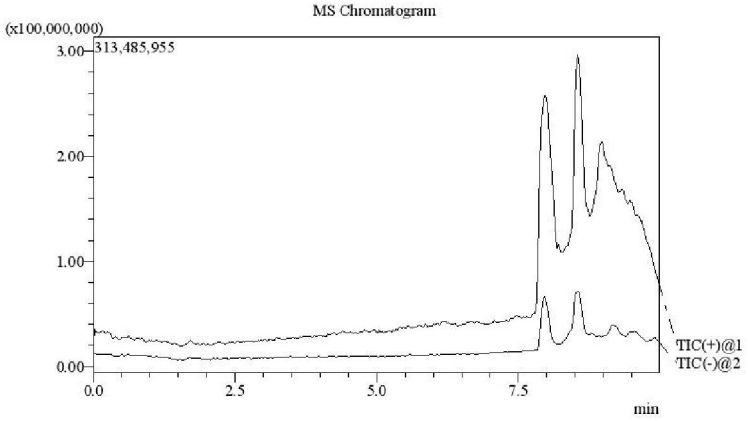

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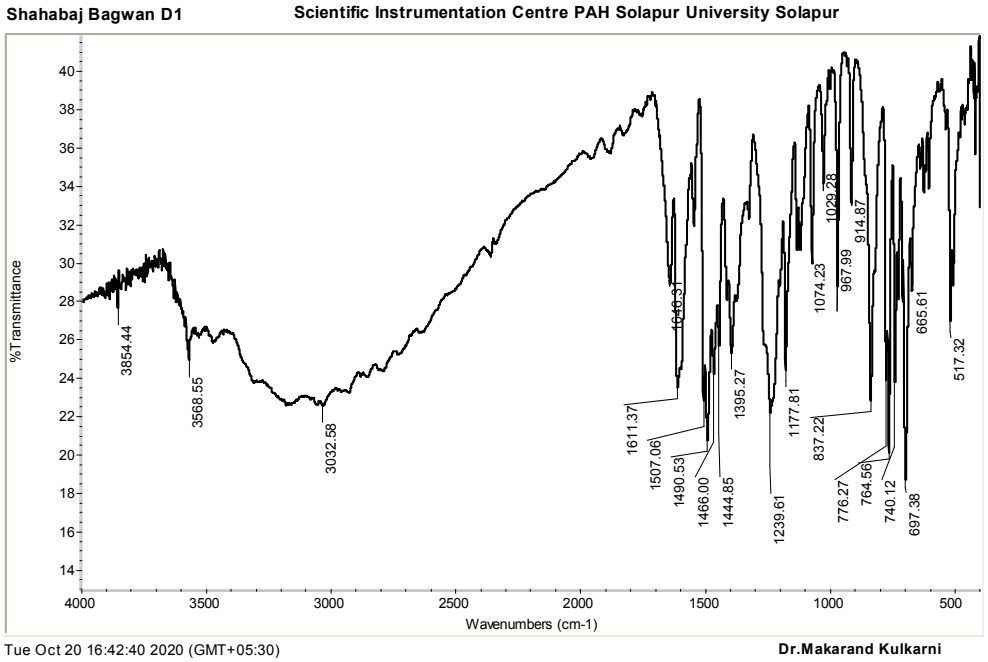
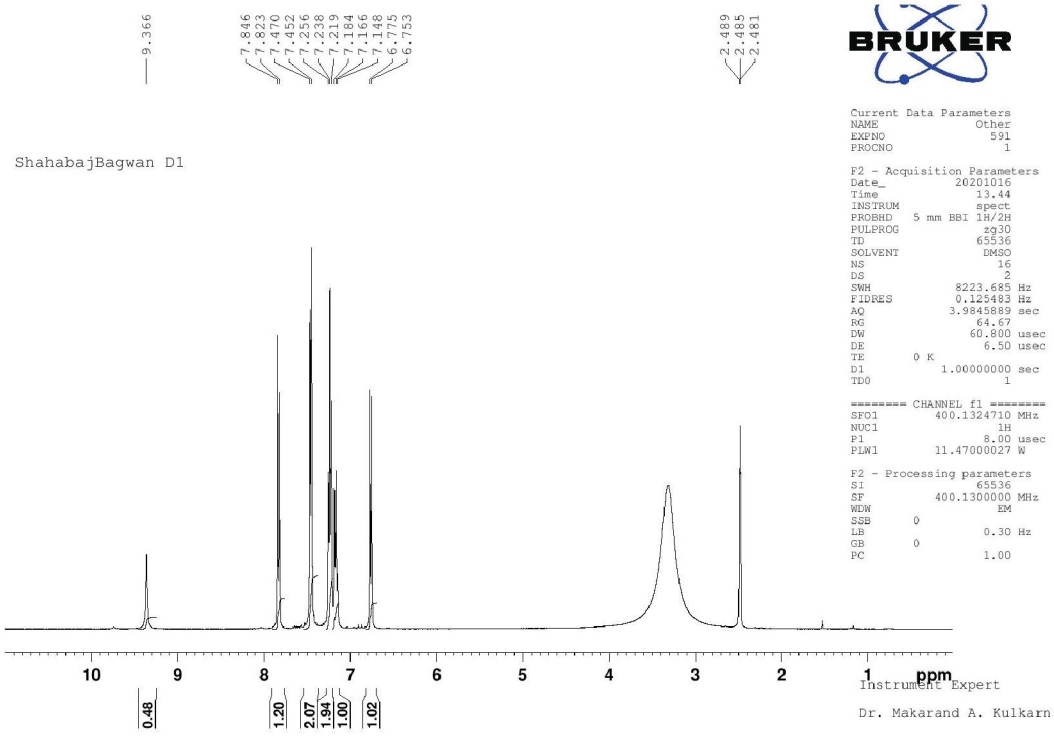
E. FT-IR Analysis 2-(4-Hydroxyphenyl)-4, 5-diphenyl-1H-Imidazole (1b):



F. ^{1}H-NMR Analysis 2-(4-Hydroxyphenyl)-4, 5-diphenyl-1H-Imidazole (1b)



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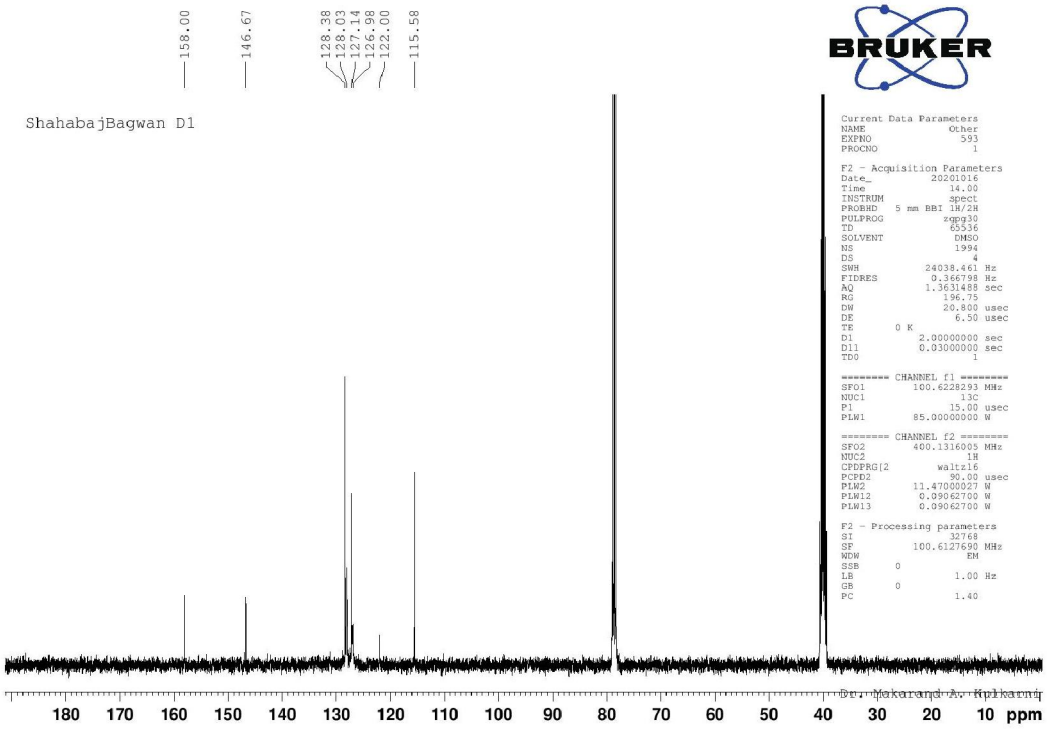
G. ^{13}C-NMR Analysis 2-(4-Hydroxyphenyl)-4, 5-diphenyl-1H-Imidazole (1b):



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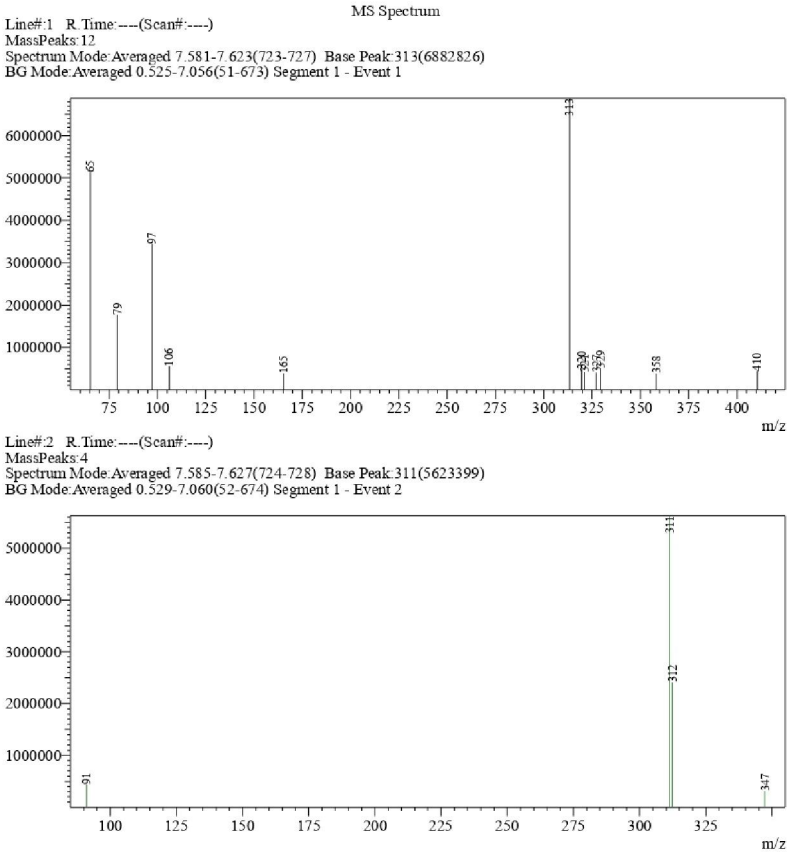
H. Mass Analysis 2-(4-Hydroxyphenyl)-4, 5-diphenyl-1H-Imidazole (1b):

SOPHISTICATED ANALYTICAL INSTRUMENT FACILITY (SAIF)
M.G.UNIVERSITY, KOTTAYAM

Summary(Data)

Sample Name	**: Sample D**
Vial#	**: 76**
Injection Volume	**: 5**
Month-Day Acquired	**: 11/4/2020**
Time Acquired	**: 10:49:56 AM**
Comment	**:**



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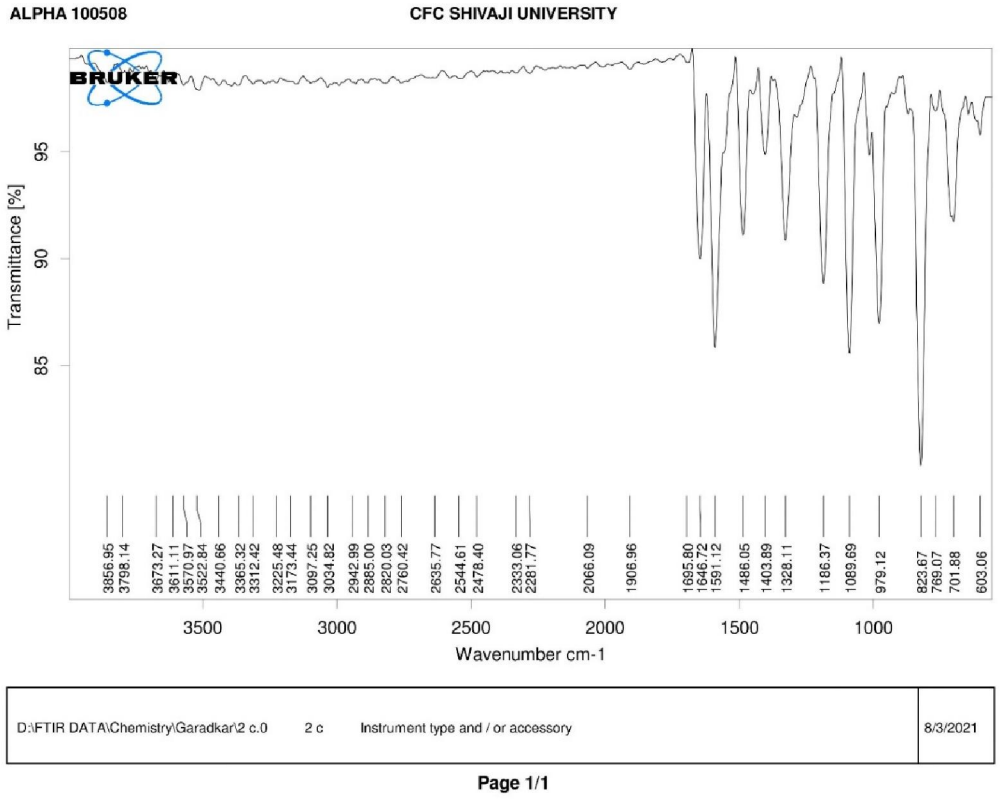
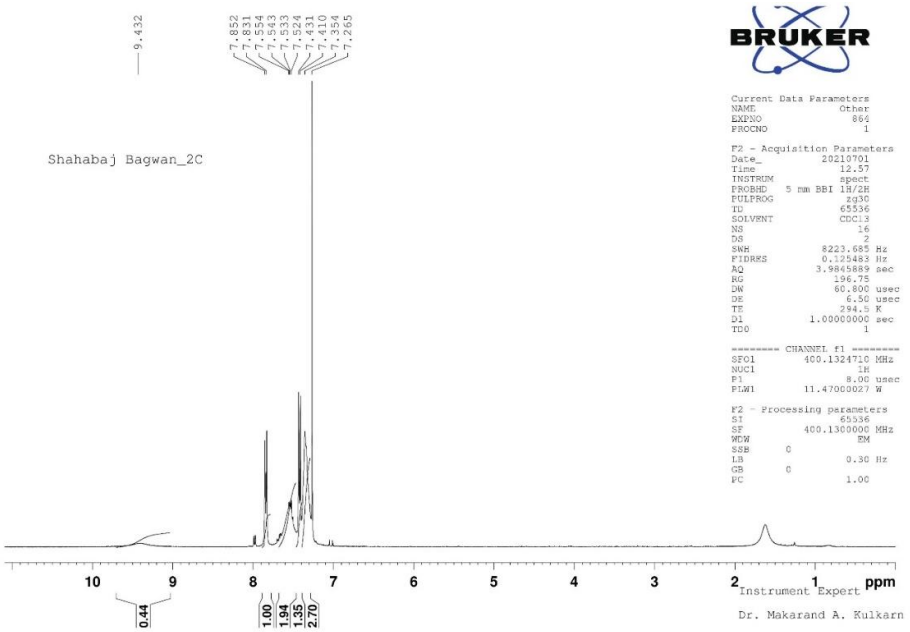
I. FT-IR Analysis 2-(4-Chlorophenyl)-4, 5-diphenyl-1H-Imidazole (1c)



J. ^{1}H-NMR Analysis 2-(4-Chlorophenyl)-4, 5-diphenyl-1H-Imidazole (1c):



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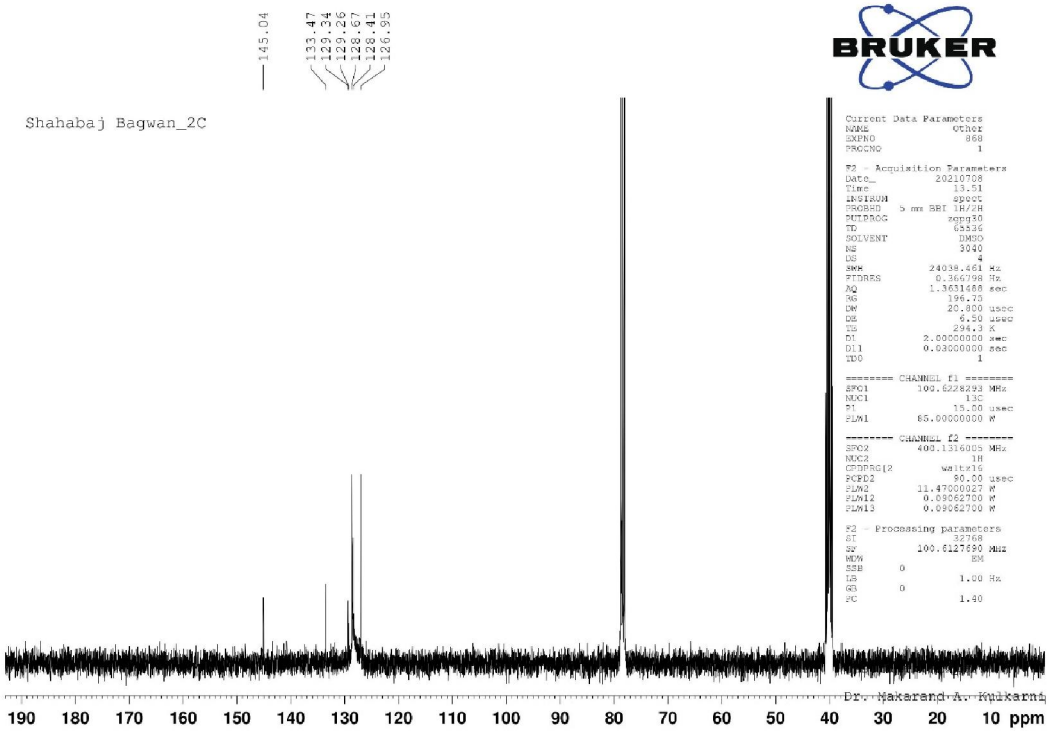
K. ^{13}C-NMR Analysis 2-(4-Chlorophenyl)-4, 5-diphenyl-1H-Imidazole (1c):



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L. Mass Analysis 2-(4-Chlorophenyl)-4, 5-diphenyl-1H-Imidazole (1c):

SOPHISTICATED ANALYTICAL INSTRUMENT FACILITY (SAIF)
M.G.UNIVERSITY, KOTTAYAM

Summary(Data)

Sample Name	**: 2c**
Vial#	**: 5**
Injection Volume	**: 5**
Month-Day Acquired	**: 7/6/2021**
Time Acquired	**: 12:42:07 PM**
Comment	**:**